## REMARKS

Claims 1, 2, 4 and 7-12 are pending.

Applicants thank the Examiner for withdrawal of the new matter and written description rejections with respect to claims 1, 2 and 4, and for withdrawal of the anticipation-based rejection of claim 1 in view of Nelson.

Applicants acknowledge that the Examiner has maintained rejections of claims 1,2, 4 and 7-12, under 35 U.S.C. § 112 ¶ 1, based on alleged lack of written description.

Applicants further acknowledge that the Examiner has maintained rejections of claims 1,2, 4, 7-12 and 13-15 under 35 U.S.C. § 112 ¶ 1, based on alleged lack of enablement.

Applicants have responsively amended the pending claims in view of the Examiner's comments, and respectfully request reconsideration of the above-identified patent application.

No new matter has been added.

### *Rejections under 35 U.S.C. § 112, ¶1*

***Written description:***

The Examiner has maintained the rejection of claims 7-12 under 35 U.S.C. § 112, ¶1, lacking sufficient written description (*Id*, at page 3, para 5).

With respect to claims 7-12, the Examiner contends that claims read on immense genus of nucleic acids, not adequately described by the Specification, in view of the fact the claims recite a probe or primer which hybridizes to any region of at least 12 contiguous nucleotides of a sequence selected from the group consisting of SEQ ID NOS:34-37 (Office Action of 24 March 2004 at page 4, second full paragraph).

Applicants have responsively amended independent claims 7 and 10 in view of the Examiner's comments. Additionally, claim 9 has been cancelled herein.

Specifically, the limits of *dependent* claim 9 (cancelled) have been incorporated into *independent* kit claim 7, which has been amended to delete the 'hybridization' language, and now recites, in (a), "comprising at least 12 contiguous nucleotides of a sequence selected from the group consisting of SEQ ID NOS:34-37, 38, complements thereof, and the bisulfite-converted sequences thereof," and further recites, in (b) "wherein the kit, based at least in part on the probe or primer, is suitable to determine the methylation status of one or more CpG dinucleotides within

the sequence selected from the group consisting of SEQ ID NOS:34-37, and 38."

The subject matter has been clarified by replacement of the allegedly over-broad hybridization language with reference to bisulifite-converted sequences to which, according to the present invention, many of the probes/primers must hybridize for puposes of the methylation assay.

Support for recitation of bisulfite-converted sequences is provided throughout the Specification, and in particular in the description of the various methylation assays described on pages 11-14 (and see, for example, line 15 of page 13, reciting "...performed using primers specific for bisufite-converted DNA....").

Independent claim 10 has been amended to delete the 'comprising' language, and now recites "*consisting* of a methylated or unmethylated polynucleotide sequence selected from the group consisting of sequences of SEQ ID NO:34, SEQ ID NO:37, SEQ ID NO:38, and the bisulfite-converted sequences thereof."

Applicants point out that the claims 7 and 8 are kit claims comprising methylation reagents, one element of which is a probe or primer as recited, and wherein the kit, based at least in part on the probe or primer, is suitable to determine the methylation status of one or more CpG dinucleotides within the sequence selected from the group consisting of SEQ ID NOS:34-37, and 38.

Applicants therefore, contend that the amended kit claims (7 and 8) and isolated nucleic acid claims (10-12) are commensurate in scope with the Specification, and respectfully request withdrawal of the Examiner's new matter rejection with respect to pending amended claims 7-12.

***Enablement:***

The Examiner maintained rejection of claims 1-2, 4, 7-12 and new claims 13-15, under 35 U.S.C. § 112, ¶1, based on lack of enablement (Office Action of 24 March 2004 at page 5).

Specifically, the Examiner alleges: (1) that the Specification "has not taught that a predictable correlation exists between nucleic acids that are 'coordinately methylated contiguous CpG island sequences that comprise a DNA sequence selected from the group consisting of SEQ

ID NOS:36 and 37'" (*Id*, last paragraph on page 6, and see page 12); and (2) that while the affidavit of Dr. Cathy Lofton-Day (of record) addresses breast cancer with respect to SEQ ID NO:36, and breast, colon and prostate cancer with respect to SEQ ID NO:37, "there is no evidence that hypermethylation of SEQ ID NO:36 is associated with colon cancer" (*Id*, page 11, second full paragraph).

Applicants have amended claims 1, 2, 13 and 14 to clarify the claimed subject matter in view of the Examiner's comments.

Specifically, *independent* claim 1 has been amended, in (b), to recite "SEQ ID NO:36" in place of SEQ ID NOS:36 and 37, and further amended to recite "breast cancer" in place of prostate, breast or colon cancer, thus deleting the association of hypermethylation of SEQ ID NO:36 and colon cancer.

Additionally, *independent* claims 1 and 13 have been amended to recite "...and coordinately *hyper*methylated contiguous CpG island sequences..." in place of coordinately methylated contiguous CpG island sequences.

This amendment addresses the Examiner's contention that it would involve undue experimentation for a skilled artisan to determine coordinately methylated contiguous CpG islands sequences that comprise SEQ ID NOS:36 or 37, and then further assay to determine whether they are hypermethylated or hypomethylated, and then further determine whether the abberant methylation status is associated with cancer.

Applicant's present amendment reciting "coordinately *hyper*methylaed contiguous CpG islands that comprise SEQ ID NO:36 or 37 addresses this issue, because applicants have already established the correlation of hypermethylation of SEQ ID NOS:36 and 37 with cancer. Therefore, recitation of coordinately hypermethylated contiguous CpG islands encompasses only those contiguous CpG island that would also correlate with the same respective cancer(s). Applicants respectfully contend that it would not entail undue experimentation to determine whether a contiguous CpG island that comprises SEQ ID NO:36 or 37 is coordinately hypermethylated. Such a CpG island is identifiable and analyzable because is contiguous to

applicants disclosed sequence. Isolation of such a CpG island sequence from a cancer tissue and determining the methylation state of one or more CpG residues therein, using standard methylation assays could be done by one of ordinary skill in the art in a matter of a few days or a week, based on applicant's disclosed sequences and teachings. This does not represent undue experimentation.

Additionally, *dependent* claim 2 has been amended to recite "SEQ ID NO:36," in place of "is a sequence selected from the group consisting of contiguous CpG island sequences that comprise a DNA sequence selected from the group consisting of SEQ ID NOS:36 and 37."

Similarly, dependent claim 14 has been amended to recite "consists of SEQ ID NO:37" in place of "is a sequence selected from the group consisting of contiguous CpG island sequences that comprise a DNA sequence selected from the group consisting of SEQ ID NO:37."

Applicants, in view of the above-described amendments and comments, respectfully request withdrawal of the Examiner's enablement rejection of amended claims 1,2, 4, 7-12 and 13-15. No new matter has been added.

***Conclusion***

In view of the foregoing amendments and remarks, applicants respectfully request reconsideration of the claimed invention, entry of the present responsive Amendment and allowance of all pending claims 1 (Currently amended), 2 (Currently amended), 4 (Previously amended), 7 (Currently amended), 8 (Previously amended), 10 (Currently amended), 11 (Original), 12 (Original), 13 (Currently amended), 14 (Currently amended) and 15 (Previously added).

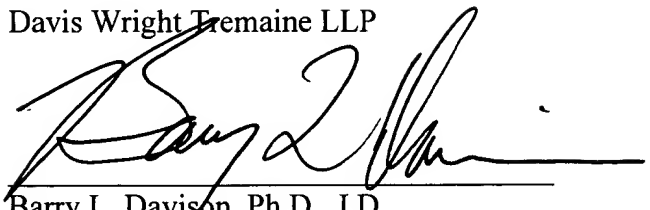
//

//

//

Respectfully submitted,

Davis Wright Tremaine LLP



Barry L. Davison, Ph.D., J.D.
Attorney for Applicant
Registration No. 47,309

Davis Wright Tremaine LLP
2600 Century Square
1501 Fourth Avenue
Seattle, Washington 98101-1688
Telephone: 206-628-7621
Facsimile: 206-628-7699